REMARKS

Claims 28-38, 55 and 56 are pending. Claims 28, 36-38, 55 and 56 are amended herein to recite that the claimed compositions consist of the recited proanthocyanidins. Claim 55 is also amended to specify that the compositions also contain a pharmaceutically acceptable carrier, diluent, or excipient and that the therapeutic amount of the proanthocyanidin is selected for efficacy in treating amyloid, α -synuclein or NAC fibrillogenesis in a mammalian subject.

Basis for this amendment may be found throughout the specification as originally filed.

EXAMINER INTERVIEW

Applicants thank Examiner Chong for the courtesy extended during the telephonic Interview on August 21, 2008. In the Interview, the patentability of claims 28-38, 55 and 56 was discussed with respect to art cited in the office action. Applicants agreed to amend the claims to recite the transitional phrase "consisting of".

REJECTION OF CLAIMS UNDER 35 U.S.C. §103(a)

The Office Action maintains the rejection of claims under 35 U.S.C. § 103(a) over various references of record. The Office Action alleges that in the instant claims the limitation "consisting essentially of" is viewed as "comprising" because the burden of stating the basic and novel characteristics of the claimed subject matter is allegedly not met. The Office Action questions how one of ordinary skill in the art would know if certain components of green tea extract would materially affect the basic and novel characteristics of tea when basic and novel characteristic of claimed subject matter is allegedly not disclosed. The Office Action further alleges that one can not distinguish between the components of green tea extract in terms of any basic or novel characteristic that is present in any one component and not present in another since all of the components are known for same purpose or therapeutic activity.

Without conceding the propriety of the rejection, but to expedite prosecution, Applicants have amended claim 28, 36-38, 55 and 56 to recite that the claimed compositions consist of the recited proanthocyanidins and a pharmaceutically acceptable carrier, diluent or excipient. Applicants reserve right to file one or more divisional and/or continuation applications directed to the canceled subject matter.

At the outset, Applicants remind the Examiner that Applicants have previously (in a response filed October 14, 2004) discussed and provided references that report the components

of green tea. Various records in the art disclose components of green tea as (+) catechin, (-) epicatechin, (-) gallocatechin, (-) gallocatechin gallate, (-) epicatechin gallate, (-) epigallocatechin, (-) catechin gallate and (-) epigallocatechin gallate.

The Legal Standard

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a). In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. at 1741, 82 USPQ2d 1396 (2007), the Supreme Court stated that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *See also* USPTO Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57,526, 57,528 (Oct. 10, 2007) ("it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.").

Thus, consistent with the principles enunciated in *KSR*, obviousness can be established by showing a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference *and* to carry out the modification with a reasonable expectation of success, viewed in light of the prior art. Both the suggestion and the reasonable expectation of success must both be found in the prior art and *not* be based on the applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

Kuznicki *et al.* (U.S. Patent No. 5,681,569)

Claims 28-38, 41 and 55-56 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kuznicki *et al.* because the cited reference allegedly teaches a composition containing green tea solids extracted from tea material. The Office Action alleges that the extract contains 0.01-0.35% flavanols and catechins, wherein the catechin or a mixture of two or

more catechins are catechin, epicatechin, gallocatechin, epigallocatechin gallate and epicatechin gallate, and a pharmaceutical carrier. The Office Action alleges that the green tea composition of Kuznicki *et al.* inherently contains proanthocyanidin oligomers having the instant formula I and II and/or procyanidins such as the dimers and trimers of catechin and epicatechin because catechins are allegedly known to encompass these compounds which are known to be isolated from green tea. The Office Action alleges that the inherency of the green tea composition is supported by the Hashimoto *et al.* and Morimoto *et al.*

Disclosure of Kuznicki *et al.*

Kuznicki *et al.* teaches compositions comprising green tea extracts. The reference describes that green tea extracts contain flavanols. It further teaches that the term flavanol or catechin means primarily catechin, epicatechins, and their derivatives (column 3, lines 20-21). The reference describes that the derivatives include sugar, salts, sugar esters, and other edible physiologically available derivatives. The reference further describes catechin, epicatechin, gallocatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate as the preferred flavanols. It is described in the reference that the flavanols used therein can be extracted from fruit, vegetables, green tea or other natural sources (column 4, lines 9-11). There is no teaching or suggestion in Kuznicki, *et al.*, to alter the green tea extract taught therein to consist of the proanthocyanidins of instant claims.

Differences between the claimed subject matter and the disclosure of Kuznicki *et al.*

Claims 28-38

Applicants respectfully submit that the cited reference describes green tea compositions containing flavanols and further discloses that the term flavanol or catechin means primarily catechin, epicatechins, and their derivatives. Kuznicki *et al.* does not disclose that the flavanols or catechins therein emcompass a proanthocyanidin, selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations of Formula I and Formula II, where n is 2-20 as claimed in claim 28. Further, the reference does not disclose that the compositions described therein consist of oligomers of catechins or epicatechins, where the oligomers contain 2-20 monomers of catechins or epicatechins or combinations of monomers of catechins or epicatechins recited in claim 28.

Further, the composition claimed in claim 28 consists of a therapeutically effective amount of a proanthocyanidin, selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations thereof, and pharmaceutically acceptable salts of the foregoing proanthocyanidins selected for efficacy in treating amyloid, α -synuclein or NAC fibrillogenesis in a mammalian subject. Since the cited reference does not teach or suggest a pharmaceutical composition consisting of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations of Formula I and Formula II, and pharmaceutically acceptable salts of the foregoing proanthocyanidins, it can not teach or suggest compositions containing therapeutic amount thereof effective for treating amyloid, α -synuclein or NAC fibrillogenesis in mammalian subjects as recited in claim 28.

Furthermore, the reference does not teach or suggest the specific therapeutic amounts or the specific proanthocyanidins claimed in dependent claims 29-38. For example, Kuznicki *et al.* does not teach or suggest a composition consisting of the procyanidins recited in claim 28 in the specific therapeutic amount of about 10 to 1,000 mg/kg body weight of the subject or 10 to 100 mg/kg body weight of the subject as claimed in the pharmaceutical compositions of claims 29 and 30, respectively. Neither does Kuznicki *et al.* teach or suggest pharmaceutical compositions consisting of the proanthocyanidin selected from the group consisting of dimers and trimers of epicatechin, epiafzelechin and catechin, and the pharmaceutically acceptable salts thereof as recited in claim 31; the procyanidin dimer epicatechin-4β→8-epicatechin recited in claim 32; the procyanidin dimer catechin-4α→8-epicatechin recited in claim 33; the procyanidin dimer epiafzelechin-4β→8-epicatechin recited in claim 34; the procyanidin trimer epicatechin-4β→8-epicatechin-4β→8-epicatechin recited in claim 35; the dimers and trimers of epicatechin, epiafzelechin and catechin, recited in claim 36; the dimers and trimers of epicatechin recited in claim 37 or a mixture of two or more of the proanthocyanidins selected from the group consisting of epicatechin-4β→8-epicatechin, catechin-4α→8-epicatechin, epiafzelechin-4β→8-epicatechin, and epicatechin-4β→8-epicatechin-4β→8-epicatechin as recited in claim 38.

Pursuant to the rule established in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), and USPTO Examination Guidelines for Determining Obviousness

Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57,526, 57,528 (Oct. 10, 2007), Kuznicki *et al.* itself must provide a reason, or the skilled person himself or herself must have some reason, to prepare the compositions consisting of a therapeutically effective amount of a proanthocyanidin, selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations of Formula I and Formula II, and pharmaceutically acceptable salts of the foregoing proanthocyanidins as recited in the instant claims. Applicants respectfully submit that no such reason has been identified in the Office Action. Therefore, the Office Action has not provided any evidence suggesting that a skilled person would be able to arrive at the claimed compositions based on the disclosure of Kuznicki *et al.*

The Office Action alleges that the inherency of the green tea composition is supported by the Hashimoto *et al.* and Morimoto *et al.* Applicants respectfully disagree.

As discussed in previous responses of August 23, 2005, March 22, 2006 and July 18, 2007, Hashimoto *et al.* teaches components of oolong tea extract in 80% aqueous acetone. The reference teaches that polyphenolic constituents in the 80% aqueous acetone extract of oolong tea include flavan-3-ol, dimeric flavan-3-ols and proanthocyanidins. The reference does not support the inherency of the green tea composition because it does not teach or suggest compositions consisting of a therapeutically effective amount of proanthocyanidins recited in the instant claims.

Morimoto *et al.* describes components of *Illicium anisatum* extract in 80% aqueous acetone. The reference teaches that the 80% aqueous acetone extract of *Illicium anisatum* contains several procyanidins, including compounds of formula I and II. The reference does not support the inherency of the green tea composition because it does not teach or suggest compositions consisting of a therapeutically effective amount of proanthocyanidins recited in the instant claims.

Applicants respectfully submits that Kuznicki *et al.* alone or in combination with Hashimoto *et al.* and Morimoto *et al.* not only fails to provide teaching or suggestion for the claimed compositions, but also any reasonable expectation that such compositions would be useful. In fact, following *KSR*, the Federal Circuit has repeatedly stressed that obviousness

determinations in the pharmaceutical arts must involve an assessment of whether a skilled artisan would have possessed a reasonable expectation of success. *See Forest*, 501 F.3d at 1269; *Takeda Chemical Industries, Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 1360-62 (Fed. Cir. 2007) (finding claimed pharmaceutical compound nonobvious because, *inter alia*, there existed "no reasonable expectation [of success] in the art.").

As discussed in detail above, Kuznicki *et al.* describes compositions comprising green tea extracts. The reference describes that the green extract comprises flavanols and further describes that catechin, epicatechin, gallocatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate as the preferred flavanols. Therefore, based on the teachings of Kuznicki *et al.*, one would not expect that the claimed compositions consisting of a therapeutically effective amount of a proanthocyanidin, selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations of Formula I and Formula II, and pharmaceutically acceptable salts of the foregoing proanthocyanidins as recited in claim 28 or the specific therapeutic amounts or the specific proanthocyanidins claimed in dependent claims 29-38 would be useful.

Therefore, the instant claims, which are directed to pharmaceutical compositions consisting of the recited proanthocyanidins, are not obvious over the teachings of Kuznicki *et al.*, either alone or in combination with Hashimoto *et al.* and Morimoto *et al.*

Claim 55-56

Claim 55 is directed to a pharmaceutical composition consisting of a therapeutically effective amount of a mixture of proanthocyanidins selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations of Formula I and Formula II, and pharmaceutically acceptable salts of the foregoing proanthocyanidins. Claim 56 depends from claim 55 and recites that the proanthocyanidins are selected from the group consisting of the dimers and trimers of epicatechin, epiafzelechin, and catechin, and the pharmaceutically acceptable salts thereof.

As discussed above, Kuznicki *et al.* teaches green tea compositions containing flavanols and further discloses that the term flavanol or catechin means primarily catechin, epicatechins, and their derivatives. Kuznicki *et al.* does not teach or suggest a pharmaceutical composition consisting of a

therapeutically effective amount of a mixture of proanthocyanidins selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations thereof, and pharmaceutically acceptable salts of the foregoing proanthocyanidins and a pharmaceutically acceptable carrier, diluent, or excipient, the therapeutic amount of the proanthocyanidin selected for efficacy in treating amyloid, α -synuclein or NAC fibrillogenesis in a mammalian subject as claimed in claim 55. Further, the reference does not teach or suggest a composition wherein one or more of the proanthocyanidins are selected from the group consisting of the dimers and trimers of epicatechin, epiafzelechin, and catechin, and the pharmaceutically acceptable salts thereof as claimed in claim 56.

As discussed above, pursuant to the rule established in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), Kuznicki *et al.* itself must provide a reason, or the skilled person himself or herself must have some reason, to prepare the claimed compositions. Applicants respectfully submit that no such reason has been identified in the Office Action. Therefore, the Office Action has not provided any evidence suggesting that a skilled person would be able to arrive at the claimed compositions based on the teaching of Kuznicki *et al.* or would have any reasonable expectation that such compositions would be useful.

Therefore, claims 55 and 56 are not obvious over the teachings of Kuznicki *et al.*, either alone or in combination with Hashimoto *et al.* and Morimoto *et al.*

JP 10245342

JP 10245342 allegedly teaches a pharmaceutical composition for diminishing the toxicity in nerve cells caused by β-amyloid protein containing a catechin or two or more of catechin such as epigallocatechin gallate and epicatechin gallate prescribed in effective amounts for diminishing the toxicity of β-amyloid protein, and a pharmaceutical carrier. The Office Action alleges that the green tea composition disclosed in the cited reference inherently contains proanthocyanidins oligomers having formula I and II and/or procyanidins such as the dimers and trimers of catechin and epicatechin because catechins are allegedly known to encompass these compounds which are known to be isolated from green tea.

As noted above, the instant claims recite pharmaceutical compositions consisting of the recited proanthocyanidins. JP 10245342 describes components of green tea extracts. As

discussed above, green tea extract is a complex mixture of various components. There is no teaching or suggestion in JP 10245342 to alter the green tea extract taught therein to consist of the proanthocyanidins of the instant claims. Nor is any such teaching within the scope of knowledge of those of skill in the art. The Office Action has not provided any evidence suggesting that a skilled person would be able to arrive at the claimed compositions based on the teaching of JP 10245342 or would have any reasonable expectation that such compositions would be useful. Therefore, instant claim 28, which is directed to a pharmaceutical composition consisting of a therapeutically effective amount of a proanthocyanidin, selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations thereof, and pharmaceutically acceptable salts of the foregoing proanthocyanidins selected for efficacy in treating amyloid, α -synuclein or NAC fibrillogenesis in a mammalian subject, is not obvious over the teachings of JP 10245342.

Furthermore, the reference does not teach or suggest the specific therapeutic amounts or the specific proanthocyanidins claimed in dependent claims 29-38. For example, JP 10245342 does not teach or suggest a composition consisting of the procyanidins recited in claim 28 in the specific therapeutic amount of about 10 to 1,000 mg/kg body weight of the subject or 10 to 100 mg/kg body weight of the subject as claimed in the pharmaceutical compositions of claims 29 and 30, respectively. Neither does JP 10245342 teach or suggest pharmaceutical compositions consisting of the proanthocyanidin selected from the group consisting of dimers and trimers of epicatechin, epiafzelechin and catechin, and the pharmaceutically acceptable salts thereof as recited in claim 31; the procyanidin dimer epicatechin-4β→8-epicatechin recited in claim 32; the procyanidin dimer catechin-4α→8-epicatechin recited in claim 33; the procyanidin dimer epiafzelechin-4β→8-epicatechin recited in claim 34; the procyanidin trimer epicatechin-4β→8-epicatechin-4β→8-epicatechin recited in claim 35; the dimers and trimers of epicatechin, epiafzelechin and catechin, recited in claim 36; the dimers and trimers of epicatechin recited in claim 37 or a mixture of two or more of the proanthocyanidins selected from the group consisting of epicatechin-4β→8-epicatechin, catechin-4α→8-epicatechin, epiafzelechin-4β→8-epicatechin, and epicatechin-4β→8-epicatechin-4β→8-epicatechin as recited in claim 38.

JP 10245342 further does not teach or suggest a pharmaceutical composition consisting of a therapeutically effective amount of a mixture of proanthocyanidins selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations thereof, and pharmaceutically acceptable salts of the foregoing proanthocyanidins and a pharmaceutically acceptable carrier, diluent, or excipient, the therapeutic amount of the proanthocyanidin selected for efficacy in treating amyloid, α -synuclein or NAC fibrillogenesis in a mammalian subject as claimed in claim 55. Neither does the reference teach or suggest a composition wherein one or more of the proanthocyanidins are selected from the group consisting of the dimers and trimers of epicatechin, epiafzelechin, and catechin, and the pharmaceutically acceptable salts thereof as claimed in claim 56.

Applicants respectfully submit that the Office Action has not provided any evidence suggesting that a skilled person would be able to arrive at the claimed compositions or would have a reason to prepare the claimed compositions based on the disclosure of JP 10245342. Furthermore, the Office Action has not provided any evidence suggesting that a skilled person would have any reasonable expectation that such compositions would be useful. Therefore, none of the pending claims are not obvious over the teachings of JP 10245342.

Hashimoto *et al.*

As discussed above, Hashimoto *et al.* teaches components of oolong tea extract **in 80% aqueous acetone**. The reference describes that polyphenolic constituents in the 80% aqueous acetone extract of oolong tea include flavan-3-ol, dimeric flavan-3-ols and proanthocyanidins. The reference does not describe any pharmaceutical compositions.

As noted above, the instant claims recite pharmaceutical compositions consisting of a therapeutically effective amount of a proanthocyanidin described in the claims and a pharmaceutically acceptable carrier, diluent, or excipient, the therapeutic amount of the proanthocyanidin selected for efficacy in treating amyloid, α -synuclein or NAC fibrillogenesis in a mammalian subject. As appreciated by the Examiner (*See,* Office Action page 8, lines 5-13) and as well known in the art, oolong tea compositions contain a complex mixture of active components. There is no teaching or suggestion in Hashimoto *et al.* to formulate a pharmaceutical composition consisting of a therapeutically effective amount of a proanthocyanidin or a mixture of proanthocyanidin as claimed herein. Nor is any such teaching

within the scope of knowledge of those of skill in the art. The Office Action has not provided any evidence suggesting that a skilled person would be able to arrive at the claimed compositions based on the teaching of Hashimoto *et al.* or would have any reasonable expectation that such compositions would be useful.

Therefore, instant claim 28, which is directed to a pharmaceutical composition consisting of a therapeutically effective amount of a proanthocyanidin, selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations thereof, and pharmaceutically acceptable salts of the foregoing proanthocyanidins selected for efficacy in treating amyloid, α -synuclein or NAC fibrillogenesis in a mammalian subject, is not obvious over the teachings of Hashimoto *et al.*

Furthermore, the reference does not teach or suggest the specific therapeutic amounts or the specific proanthocyanidins claimed in dependent claims 29-38. For example, Hashimoto *et al* does not teach or suggest a composition consisting of the procyanidins recited in claim 28 in the specific therapeutic amount of about 10 to 1,000 mg/kg body weight of the subject or 10 to 100 mg/kg body weight of the subject as claimed in the pharmaceutical compositions of claims 29 and 30, respectively. Neither does Hashimoto *et al* teach or suggest pharmaceutical compositions consisting of the proanthocyanidin selected from the group consisting of dimers and trimers of epicatechin, epiafzelechin and catechin, and the pharmaceutically acceptable salts thereof as recited in claim 31; the procyanidin dimer epicatechin-4β→8-epicatechin recited in claim 32; the procyanidin dimer catechin-4α→8-epicatechin recited in claim 33; the procyanidin dimer epiafzelechin-4β→8-epicatechin recited in claim 34; the procyanidin trimer epicatechin-4β→8-epicatechin-4β→8-epicatechin recited in claim 35; the dimers and trimers of epicatechin, epiafzelechin and catechin, recited in claim 36; the dimers and trimers of epicatechin recited in claim 37 or a mixture of two or more of the proanthocyanidins selected from the group consisting of epicatechin-4β→8-epicatechin, catechin-4α→8-epicatechin, epiafzelechin-4β→8-epicatechin, and epicatechin-4β→8-epicatechin-4β→8-epicatechin as recited in claim 38.

Hashimoto *et al* further does not teach or suggest a pharmaceutical composition consisting of a therapeutically effective amount of a mixture of proanthocyanidins selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins

characterized by oligomeric combinations thereof, and pharmaceutically acceptable salts of the foregoing proanthocyanidins and a pharmaceutically acceptable carrier, diluent, or excipient, the therapeutic amount of the proanthocyanidin selected for efficacy in treating amyloid, α - synuclein or NAC fibrillogenesis in a mammalian subject as claimed in claim 55. Neither does the reference teach or suggest a composition wherein one or more of the proanthocyanidins are selected from the group consisting of the dimers and trimers of epicatechin, epiafzelechin, and catechin, and the pharmaceutically acceptable salts thereof as claimed in claim 56.

Applicants respectfully submit that the Office Action has not provided any evidence suggesting that a skilled person would be able to arrive at the claimed compositions or would have a reason to prepare the claimed compositions based on the disclosure of Hashimoto *et al.* Furthermore, the Office Action has not provided any evidence suggesting that a skilled person would have any reasonable expectation that such compositions would be useful. Therefore, none of the pending claims are not obvious over the teachings of Hashimoto *et al.*

Morimoto *et al.*

Morimoto *et al.* describes isolation and structural elucidation of components of *Illicium anisatum*. The reference teaches extracts of bark of *Illicium anisatum* in 80% aqueous acetone. The reference teaches that the 80% aqueous acetone extract contains several procyanidins, including compounds of formula I and II. The reference does not teach or suggest pharmaceutical compositions.

As noted above, the instant claims recite pharmaceutical compositions consisting of the recited proanthocyanidins. Applicants direct Examiner's attention to the fact that Morimoto *et al.* is directed to isolation and structural elucidation of components of *Illicium anisatum*. As described in the reference, several compounds were isolated from the 80% acetone extract (*see,* Abstract and page 908 and 910). The reference does not teach or suggest pharmaceutical compositions containing any of the compounds. There is no teaching or suggestion in Morimoto *et al.* to formulate a pharmaceutical composition consisting of a therapeutically effective amount of a proanthocyanidin or a mixture of proanthocyanidin as claimed herein. Nor is any such teaching within the scope of knowledge of those of skill in the art. The Office Action has not provided any evidence suggesting that a skilled person would be able to arrive at the claimed

compositions based on the teaching of Morimoto *et al.* or would have any reasonable expectation that such compositions would be useful.

Therefore, instant claim 28, which is directed to a pharmaceutical composition consisting of a therapeutically effective amount of a proanthocyanidin, selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations thereof, and pharmaceutically acceptable salts of the foregoing proanthocyanidins selected for efficacy in treating amyloid, α -synuclein or NAC fibrillogenesis in a mammalian subject, is not obvious over the teachings of Morimoto *et al.*

Furthermore, the reference does not teach or suggest the specific therapeutic amounts or the specific proanthocyanidins claimed in dependent claims 29-38. For example, Morimoto *et al* does not teach or suggest a composition consisting of the procyanidins recited in claim 28 in the specific therapeutic amount of about 10 to 1,000 mg/kg body weight of the subject or 10 to 100 mg/kg body weight of the subject as claimed in the pharmaceutical compositions of claims 29 and 30, respectively. Neither does Morimoto *et al* teach or suggest pharmaceutical compositions consisting of the proanthocyanidin selected from the group consisting of dimers and trimers of epicatechin, epiafzelechin and catechin, and the pharmaceutically acceptable salts thereof as recited in claim 31; the procyanidin dimer epicatechin-4β→8-epicatechin recited in claim 32; the procyanidin dimer catechin-4α→8-epicatechin recited in claim 33; the procyanidin dimer epiafzelechin-4β→8-epicatechin recited in claim 34; the procyanidin trimer epicatechin-4β→8-epicatechin-4β→8-epicatechin recited in claim 35; the dimers and trimers of epicatechin, epiafzelechin and catechin, recited in claim 36; the dimers and trimers of epicatechin recited in claim 37 or a mixture of two or more of the proanthocyanidins selected from the group consisting of epicatechin-4β→8-epicatechin, catechin-4α→8-epicatechin, epiafzelechin-4β→8-epicatechin, and epicatechin-4β→8-epicatechin-4β→8-epicatechin as recited in claim 38.

Morimoto *et al* further does not teach or suggest a pharmaceutical composition consisting of a therapeutically effective amount of a mixture of proanthocyanidins selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations thereof, and pharmaceutically acceptable salts of the foregoing proanthocyanidins and a pharmaceutically acceptable carrier, diluent, or excipient, the

therapeutic amount of the proanthocyanidin selected for efficacy in treating amyloid, α - synuclein or NAC fibrillogenesis in a mammalian subject as claimed in claim 55. Neither does the reference teach or suggest a composition wherein one or more of the proanthocyanidins are selected from the group consisting of the dimers and trimers of epicatechin, epiafzelechin, and catechin, and the pharmaceutically acceptable salts thereof as claimed in claim 56.

Applicants respectfully submit that the Office Action has not provided any evidence suggesting that a skilled person would be able to arrive at the claimed compositions or would have a reason to prepare the claimed compositions based on the disclosure of Morimoto *et al.* Furthermore, the Office Action has not provided any evidence suggesting that a skilled person would have any reasonable expectation that such compositions would be useful. Therefore, none of the pending claims are not obvious over the teachings of Morimoto *et al.*

Hatano et al.

Hatano *et al.* describes eight tannins isolated from the leaf of *Camellia japonica.* The reference further describes that the tannins isolated include complex tannins consisting of monomeric hydrolysable tannin and epicatechin, dimeric hydrolysable tannins and complex tannins composed of a dimeric hydrolysable tannin and epicatechin. The reference further describes that the tannins isolated showed anti-HIV activity. The Office Action urges that the compositions in the cited reference inherently contains the instant compounds because these compounds are known to be isolated from *Camellia japonica* plants. The Office Action acknowledges that the reference does not specifically disclose a pharmaceutical composition consisting essentially of a therapeutically effective amount of a proanthocyanidin of formula I or II. However it is alleged that it would have been *prima facie* obvious to a person of ordinary skill in the art to have optimized the amount of the active agent so as to formulate a pharmaceutical compositions consisting essentially of a therapeutically effective amount of a proanthocyanidin of formula I or II. The Office Action further alleges that one of ordinary skill in the art would have been motivated to formulate a pharmaceutical compositions consisting essentially of a therapeutically effective amount of a proanthocyanidin of formula I or II because proanthocyanidin of formula I or II is allegedly disclosed in the reference and it is allegedly obvious to optimize the amount when the general conditions are given.

As noted above, the instant claims recite pharmaceutical compositions consisting of the recited proanthocyanidins. As appreciated by the Examiner, *see,* Office Action page 10, last paragraph, the compositions of Hatano *et al.* contain a complex mixture of active components, including complex tannins. There is no teaching or suggestion in Hatano *et al.* to alter the compositions taught therein to arrive at a composition consisting of the proanthocyanidins of the instant claims. Nor is any such teaching within the scope of knowledge of those of skill in the art. The Office Action has not provided any evidence suggesting that a skilled person would be able to arrive at the claimed compositions based on the teaching of Hatano *et al.* or would have any reasonable expectation that such compositions would be useful.

Therefore, instant claim 28, which is directed to a pharmaceutical composition consisting of a therapeutically effective amount of a proanthocyanidin, selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations thereof, and pharmaceutically acceptable salts of the foregoing proanthocyanidins selected for efficacy in treating amyloid, α -synuclein or NAC fibrillogenesis in a mammalian subject, is not obvious over the teachings of Hatano *et al.*

Furthermore, the reference does not teach or suggest the specific therapeutic amounts or the specific proanthocyanidins claimed in dependent claims 29-38. For example, Hatano *et al* does not teach or suggest a composition consisting of the procyanidins recited in claim 28 in the specific therapeutic amount of about 10 to 1,000 mg/kg body weight of the subject or 10 to 100 mg/kg body weight of the subject as claimed in the pharmaceutical compositions of claims 29 and 30, respectively. Neither does Hatano *et al* teach or suggest pharmaceutical compositions consisting of the proanthocyanidin selected from the group consisting of dimers and trimers of epicatechin, epiafzelechin and catechin, and the pharmaceutically acceptable salts thereof as recited in claim 31; the procyanidin dimer epicatechin-4β→8-epicatechin recited in claim 32; the procyanidin dimer catechin-4α→8-epicatechin recited in claim 33; the procyanidin dimer epiafzelechin-4β→8-epicatechin recited in claim 34; the procyanidin trimer epicatechin-4β→8-epicatechin-4β→8-epicatechin recited in claim 35; the dimers and trimers of epicatechin, epiafzelechin and catechin, recited in claim 36; the dimers and trimers of epicatechin recited in claim 37 or a mixture of two or more of the proanthocyanidins selected from the group

consisting of epicatechin-4β→8-epicatechin, catechin-4α→8-epicatechin, epiafzelechin-4β→8-epicatechin, and epicatechin-4β→8-epicatechin-4β→8-epicatechin as recited in claim 38.

Hatano *et al* further does not teach or suggest a pharmaceutical composition consisting of a therapeutically effective amount of a mixture of proanthocyanidins selected from a group of proanthocyanidins characterized by Formula I or Formula II, and proanthocyanidins characterized by oligomeric combinations thereof, and pharmaceutically acceptable salts of the foregoing proanthocyanidins and a pharmaceutically acceptable carrier, diluent, or excipient, the therapeutic amount of the proanthocyanidin selected for efficacy in treating amyloid, α - synuclein or NAC fibrillogenesis in a mammalian subject as claimed in claim 55. Neither does the reference teach or suggest a composition wherein one or more of the proanthocyanidins are selected from the group consisting of the dimers and trimers of epicatechin, epiafzelechin, and catechin, and the pharmaceutically acceptable salts thereof as claimed in claim 56.

Applicants respectfully submit that the Office Action has not provided any evidence suggesting that a skilled person would be able to arrive at the claimed compositions or would have a reason to prepare the claimed compositions based on the disclosure of Hatano *et al.* Furthermore, the Office Action has not provided any evidence suggesting that a skilled person would have any reasonable expectation that such compositions would be useful. Therefore, none of the pending claims are not obvious over the teachings of Hatano *et al.*

CONCLUSION

Applicants reiterate that consistent with the principles enunciated in *KSR*, obviousness can be established by showing a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference *and* to carry out the modification with a reasonable expectation of success, viewed in light of the prior art. Applicants respectfully submit that none of the cited reference, either alone or in combination, teaches or suggests the claimed pharmaceutical compositions consisting of the recited proanthocyanidins. Nor do the references provide reasonable expectation that the claimed compositions would be useful. Therefore, the claimed compositions are not obvious over the cited references.

In light of the above remarks, the Applicants respectfully request that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Applicant hereby petitions under 37 C.F.R. §1.136 for two (2) months extension of time. Please apply fees for the extension of time and any other charges, or any credits, to Deposit Account 50-3013. The Commissioner is hereby authorized to charge any other required fee(s) to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: September 2, 2008

By: Megha Bhumralkar (Reg. no. 44,536)
For: Dale L. Rieger (Reg. No. 43,045)
JONES DAY
222 East 41st Street
New York, New York 10017
858.314.1200